

The Finnish decision-making process to recommend a new vaccine: From vaccine research to vaccination policy

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Abstract

Aim This article takes a closer look at the decision-making process to recommend a new vaccine in the light of the Finnish experience.

Subject and methods The criteria for evidence-based knowledge are examined in order to consider how public health decision-making in the area of immunisation evolves over time and from one context to the other on the basis of three of the more recent childhood vaccines (*Haemophilus influenzae* type b (Hib), seven-valent pneumococcal conjugate (PCV-7), and Human Papilloma Virus (HPV)).

Results In the case of Hib vaccine, epidemiological research concerning both direct and indirect population protection was the driving force for implementation. By contrast, PCV-7 universal vaccination was not implemented on the basis of unfavourable cost-effectiveness evaluation. However, as this evaluation took place very early on, the cost-effectiveness analysis did not consider any indirect herd effects. Regarding the HPV vaccine, it is at present considered that cervical cancer will be better prevented by enhancing the already successful PAP smear screening programme.

Conclusion Surveillance and research are valuable tools for modern vaccine programme design. Market forces and advocacy groups strongly drive the development and implementation of new vaccines, meaning that impartial and evidence-based decision-making is essential to vaccine introduction into national programmes. At the same time, economic analyses are occupying an increasingly important

place in this decision-making. Vaccine costs are not necessarily compared to government expenditure on illness and disease. From a moral point of view, it should not be forgotten that children ought to have the right to best available health.

Keywords Decision making · Health economics · *Haemophilus influenzae* type b vaccine · Pneumococcal conjugate vaccine · Human papilloma virus vaccine

Introduction

National vaccination programmes in European Union member states vary considerably regarding antigenic composition and schedule as Lopalco (Lopalco, 2008) and Schmitt (Schmitt et al. 2003) have already pointed out. There are several explanations for this. Historical reasons combine with reasons related to the country's specific health-care delivery system and funding mechanisms; these, in turn, are influenced by current common knowledge of vaccinology arising from both national and international evidence and scientific reports. There are major variations on how such knowledge and evidence are taken into consideration and used in the context of programme design and decision-making. In Finland, national vaccination programme-related research and surveillance are co-ordinated within the national public health system and form a firm platform on which vaccine programme-related decisions are made (Fig. 1).

Ideally, those in charge of developing a national vaccination programme need to think of the right questions to ask and communicate them to those in charge of and financing research and surveillance.

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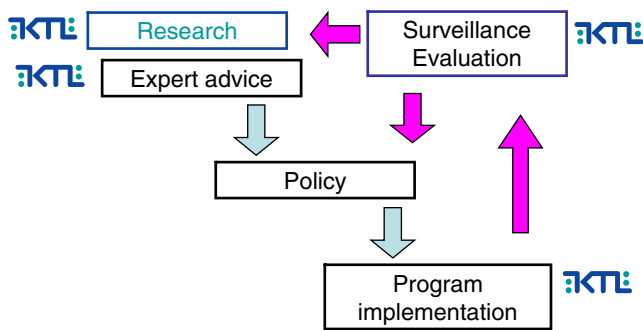


Fig. 1 Protecting the population with vaccination. The relation of surveillance, research, decision-making, and implementation, and the role of the National Public Health Institute (KTL)

It is essential to choose the right methodology when wishing to come up with programmatically useful answers. Well set up and sufficiently sensitive surveillance systems with sufficiently specific case definitions along with targeted epidemiological studies shed light on whether the disease can be considered a public health problem. Vaccine immunology studies guide in finding optimal doses and schedules provided serological correlates of protection exist; they also alert to possible interferences if several vaccines are combined or given simultaneously. They also give an understanding on the reactogenicity of the product. Vaccine efficacy trials are usually required for regulatory and licensure purposes. Vaccine effectiveness studies thereafter will provide answers as to whether the disease actually is vaccine preventable in the intended target groups. Vaccine safety is thoroughly addressed in clinical trials for licensure. However, rare adverse events are often identified only after a large number of doses has been administered, i.e., subsequent to widespread use of the vaccine. Thus, reports on adverse events and record linkage studies impart additional important safety knowledge. The need to know well in advance the impact of different vaccination scenarios has promoted the development and use of advanced tools of mathematical modelling. Simulation models can provide insights in silica as to whether wide-scale vaccination could have adverse and/or positive indirect effects on the population level in the long run. An increasingly important line of modelling is provided by health economics when considering whether vaccination could be cost-effective in a given setting.

The key questions a vaccine programme designer needs to ask are:

- Is the disease a public health problem?
- Is the disease vaccine preventable?
- How does the vaccine work?
- Is the vaccine safe?
- Could wide-scale vaccinations have adverse or positive indirect effects on the population level?
- Would vaccination be cost-effective?

Research driving vaccine implementation—the example of the Hib vaccine

In Finland, vaccine research has been an essential part of programme design for decades. The development of a *Haemophilus influenzae* type b (Hib) conjugate vaccine serves as a good demonstration case. Studies and clinical trials were carried out in Finland as early as in the 1980s–1990s (Eskola et al. 1992a, b). The baseline surveillance study among children under 5 years of age identified the incidence of Hib disease (52/100,000) as well as its clinical spectrum. The majority of cases presented as meningitis and epiglottitis (Takala et al. 1989). The baseline study was utilised to fine-tune the laboratory infrastructure required to initiate a nationwide phase III individual randomised controlled trial, which eventually demonstrated not only the high direct clinical efficacy of the diphtheria toxoid conjugated Hib vaccine (Eskola et al. 1990), but also the indirect protective impact of the vaccine, a ground-breaking observation (Eskola et al. 1996) (Fig. 2). The latter property of the vaccine was due to the reduction of the oropharyngeal carriage of the bacterium (Takala et al. 1989) and was soon evident given the decrease in disease incidence among those not vaccinated. In conjunction with the efficacy trial, several phase II immunogenicity studies were conducted in order to better understand the immunological properties and functional mechanisms of the various Hib vaccines.

In 1993, after the completion of the series of efficacy studies during which most Finnish infants had received Hib vaccine according to age, the Hib vaccine was introduced into the national immunisation programme, i.e., given to all children in Finland from 3 months of age onwards. This decision was made in the absence of any formal cost-efficacy calculations and without major disputes among stakeholders.

A clinical trial did not secure implementation into the programme—the example of pneumococcal conjugate vaccine

The enhanced surveillance system of invasive childhood diseases established for carrying out the Hib vaccine studies provided a firm network and basis of national knowledge on other causative bacterial agents among children (Saarinen et al. 1995). The gate keeping and development of the notification system were transferred from the Medical Board to the National Public Health Institute (Kansanterveyslaitos, KTL), which was charged with establishing a computer-based national communicable disease registry. For pneumococcus, special surveillance studies aimed at understanding pneumonia (Jokinen et al. 1993) and acute otitis media (Kilpi et al. 2001) complemented the data arising from the national

Invasive Hib disease, cases/year

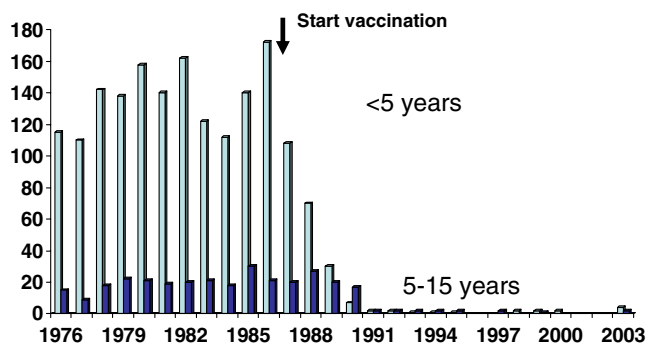


Fig. 2 The impact of Hib vaccination on the vaccinated age groups (i.e., direct effect) and those beyond the target age group (i.e., the so-called indirect herd effect). According to Eskola et al. (Rev Med Microbiol 1996; 7: 231–241) and the National Infectious Disease Register

surveillance system. It became evident that with the relatively low incidence rates of invasive pneumococcal disease among children (Eskola et al. 1992a, b), a phase III clinical trial with the endpoint of invasive pneumococcal disease would be an immense nationwide undertaking. Instead, the researchers agreed on a smaller pre-licensure trial with originally three new pneumococcal conjugate vaccines to be carried out to address a clinically less severe endpoint: otitis media. In Finland otitis media actually caused a much greater public health disease burden. This trial established the mean serotype-specific efficacy of 57% of the two candidate vaccines licensed (Eskola et al. 2001; Kilpi et al. 2003) and also provided important information on the disease burden itself. After the trial, however, seven-valent pneumococcal conjugate vaccine (PCV-7) did not make it to the national programme. Why not? How did this happen? Most professionals and lay persons alike were perplexed. What had changed between the 1990s and 2000?

From expert advice to policy formation-What changed between the 1990s and 2000?

At the turn of the present century several new paediatric vaccines became available on the market. Of these, both the rotavirus vaccine and pneumococcal conjugates were studied in Finland as part of the manufacturers phase III licensure trials (Eskola et al. 2001; Kilpi et al. 2005; Joensuu et al. 1997). It was no longer self-evident, however, that all these efficacious vaccines could be adopted by the national programme without going through a process of formal consideration, completely detached from the investigators' own interests. Also, the higher cost of the vaccines called for a thorough economic analysis. In face of the increasing public and professional demand that health policies and guidelines of all kinds be based as much as possible on scientifically sound evidence, this without doubt also applied to the introduction of any new vaccine.

In 2000, a national advisory committee for vaccination (Kansallinen rokotusasiiantuntijaryhmä, KRAR) was formed that commissioned vaccine-specific expert groups to help evaluate the scientific evidence on the basis of which the new vaccine was to be introduced (Fig. 3) (Rapola 2007). To standardise these expert evaluations, KRAR agreed on a “four-step” approach. In order to be considered for financing from the national health budget, the following four criteria had to be met:

- (1) Public health benefit, i.e., there should be a considerable disease burden, and vaccination should be expected to alleviate this burden;
- (2) Vaccine safety on the individual level, i.e., the risks of vaccination to an individual should be minimal and outweighed by the expected health benefits;
- (3) Vaccine safety on the population level, i.e., wide-scale vaccination should not have major adverse effects on the population in short or long term;

Fig. 3 Decision-making structures of the National Immunisation Programme in Finland at the beginning of the 21st century

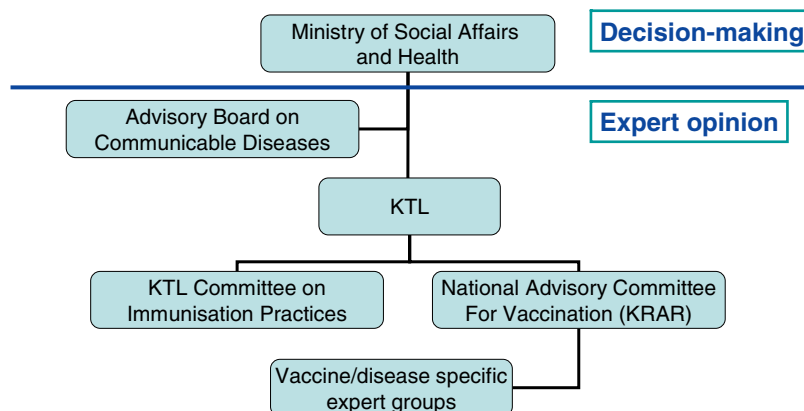


Table 1 Pneumococcal disease burden in children <5 years of age in Finland and episodes assumed to be averted by vaccination with the seven-valent pneumococcal conjugate vaccine in a mean annual birth cohort of 55,000 children as reported in 2002

Disease	Number of episodes/year	Reference	Vaccine efficacy	Reference	Number of episodes averted by PCV
Blood and/or CSF culture positive pneumococcal disease	70	National Communicable Disease Registry	89.1	Black et al. 2000	60
Pneumonia	8,000	Jokinen et al. 1993	17.7	Black et al. 2000	1,400
Acute otitis media	250,000	Eskola et al. 2001	6.0	Eskola et al. 2001	15,000
Otologic surgery procedures	15,000	National Registry	20.3	Black et al. 2000	3,000
Death	1	Klements et al. 2004	NA	NA	0.9

NA = not available

- (4) Cost-effectiveness, i.e., the intervention should be sufficiently cost-effective from the societal point of view as the universal vaccination programme is completely shouldered by the Finnish government.

Despite the licensure trials having been carried out in the country, PCV-7 was scrutinised according to the “four-step” approach. For the evaluation task, the vaccine expert group accessed local disease burden data via the national communicable disease registry and combined it with trial-related data on both burden and efficacy (Table 1). Based on the 2000 costing figures, in an annual birth cohort of 55,000 infants, the cost effectiveness analysis indicated when considering the direct effects alone, investing 12.0 million € would save annually 6.3 million € in medical and 2.0 million € in productivity and other costs. Therefore, investing 1 million € in a vaccination programme would return 0.53 million € in medical costs and 0.70 million € in societal costs. In the base case, vaccination would cost

society 134,986 € per life year saved (LYS). To achieve cost savings from a health-care provider (societal) perspective, the price of PCV-7 should be 50% (70%) of the price used in the base case. In other words, PCV-7 did not avert enough cases and deaths in comparison to the predicted costs when given as a four-dose schedule, assuming similar vaccine efficacy point prevalence values as in the US trials for invasive disease and otitis complications and in the Finnish trials for acute otitis media-related events (Salo et al. 2005).

The cost-effectiveness analysis at that time did not take into consideration the possibility of the serotype replacement phenomenon or the indirect herd protection of PCV-7 in averting disease in the non-vaccinated age groups (Anonymous, 2005) as very little data beyond the proof of reduction of upper respiratory carriage of pneumococcus (Dagan et al. 1996) was then available. As a result of an early, and in retrospect a very conservative evaluation, PCV-7 was not introduced into the Finnish immunisation programme on the universal level; it was recommended to be

Table 2 The recent evaluations and changes made in the Finnish national immunisation programme since 2000-as suggested by the National Advisory Committee for Vaccines (KRAR)

Year	Vaccine	Type of change	Target group	Evaluation included formal economic analysis	Reference
2001	Pneumococcal conjugate	Introduction	To risk groups <5 years only	Yes	Salo et al. 2005
2002	Influenza	Introduction	Elderly >65	No	CR
2003	DTaP/dtap	Introduction	6 year olds	No	CR
2005	DTaP-IPV-Hib	Introduction	All infants at 3, 5, 12 months	No	CR
2006	Tick Borne Encephalitis	5-year campaign	>7 years old living permanently on Åland	Yes	CR
2006	Bacillus Calmette Guerin	Restriction	Only to risk group newborns*	Yes	CR
2007	Influenza	Introduction	3–35-month-old children	Yes	Salo et al. 2006
2007	Rotavirus	Introduction	Before 4 months	Yes	Salo et al. 2007
2008	Pneumococcal conjugate	Introduction	TBD	Yes	NA
2008	Varicella	Introduction	TBD	Yes; ongoing	NA
2009	Human Papilloma Virus	Introduction	TBD	Yes; ongoing	NA

*Previously was given to all newborns

CR = Expert Committee Report (in Finnish language, available from the KTL website www.ktl.fi)

NA = not yet available

TBD = to be decided

given to risk group children only (Nohynek et al. 2005). A new evaluation including potential herd effects and replacement phenomenon, and calculating impact in quality-adjusted life years (QALY) in addition to LYS, is nearing completion, after which the earlier negative decision will soon be revisited.

What will happen in the future—the example of Human Papilloma Virus-vaccine in preventing cervical cancer

Similarly to the PCV-7 evaluation, several other vaccine antigens have been considered for introduction, reduction or campaign for a limited time period. Table 2 summarises the recent changes in the Finnish national immunisation programme and ongoing evaluations initiated by KRAR since 2000. Since the first PCV-7 evaluation, three other vaccines have gone through the critical four-step process. The cost effectiveness evaluation for all these three, i.e., TBE, influenza and rota vaccines, utilising local disease burden and health-care costing data has been favourable (Salo et al. 2006, 2007), unlike in many other European countries, and accordingly, they have been or will be introduced into the national programme.

It goes without saying that evidence-based decision making is here to stay. From 2001 to 2005, the annual national budget for vaccines doubled from 5 to 10 million euros. With all the expected changes (Table 2, i.e., introduction of influenza, rota, varicella, pneumococcus and human papilloma virus vaccines), the budget would increase more than four-fold, up to 43 million euros.

Whether the four-step approach is extensive and fair enough is a matter of present debate. Market forces strongly drive new childhood vaccines, keen on having them used by as many children as possible. When professionals are not in full agreement and decision-making processes slow down, the pharmaceutical industry targets common people raising disease and problem-specific awareness with their advertising campaigns and approaches of opinion leaders and politicians. Sometimes these initiatives can be quite imaginative, taking advantage of parental feelings of guilt and general concerns of health. On the other hand one should not forget that children should have the right to optimal health as declared by the United Nations Special Conference for Children in 2002.

An example of a heated debate on a new vaccine introduction is provided by the present situation of the Human Papilloma Virus (HPV) vaccines in Finland. According to the Finnish Cancer Registry, approximately 150 new cervical cancer cases are detected annually, mostly in women above 25 years of age. Simultaneously 60 deaths are caused by cervical cancer, 90% of which occur in women over 50 years of age. According to the present data,

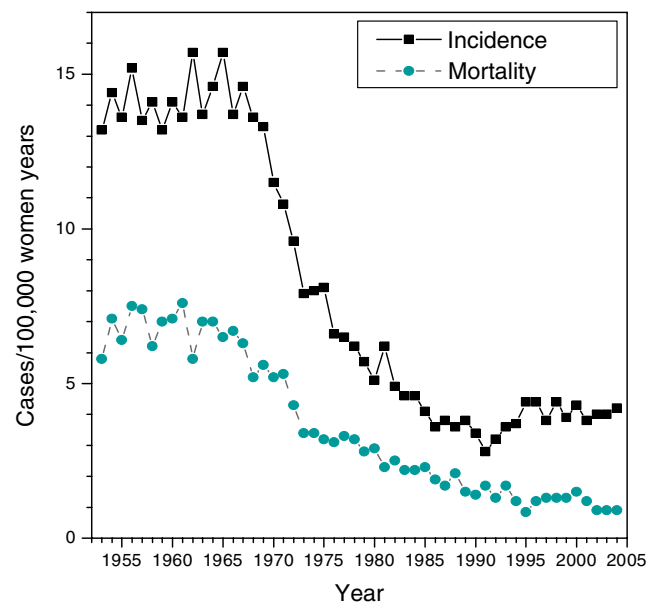


Fig. 4 Age-standardised incidence and mortality of cervical cancer in Finland since 1953

vaccinating girls above 12 years could reduce cervical cancer incidence after 20 years and deaths after 40 years of follow-up. With the experience of the rapid, world-record reduction of cervical cancer screening in Finland since the introduction of the PAP smear screening programme in year 1953 (Fig. 4), the present thinking on the national level is to intensify the already highly successful PAP smear screening. Intensifying screening especially in the younger age groups would most likely have a positive impact on these morbidity and mortality figures much faster than introducing an HPV vaccine, given the fact that the reported overall vaccine efficacy figures of HPV on cervical precancerous lesions

Table 3 The universal vaccination programme of children in Finland in 2008

Age	Vaccine
3 months	DtaP-Hib-IPV ^a
5 months	DtaP-Hib-IPV
12 months	DtaP-Hib-IPV
14–18 months	MMR ^b
4 years	DtaP-Hib-IPV
6 years	MMR ^b
14–15 years	Dtap ^c
6–35 months	Influenza, annual

^a D = diphtheria, T = tetanus, P = pertussis, polio, Hib = Haemophilus influenzae type b

^b M = measles, M = mumps, R = rubella

^c Booster dose, small letters indicating lower amount of antigens

The only addition since 2005 is the annual influenza vaccination of children 6–35 months of age. BCG, HBV and tick-borne encephalitis vaccines are given to risk group children only. Vaccines to prevent from foreign travel-related infections are not covered by the universal vaccination programme (<http://www.ktl.fi>).

caused by all HP viruses is only 27% in non-naïve individuals and that introduction of a vaccine would not bring about savings in the form of reducing screening costs. A multidisciplinary HPV expert group will be called upon to look into detail in these issues and suggest actions to be taken by the government and various stakeholders.

There are increasingly critical voices questioning to what extent economic analyses should be given weight in the decision-making processes. One of the arguments posed is a moral one: children should have the right to the best available health regardless of price. As a consequence, access to new vaccines is seen as part of the rights of a child that a nation should fulfil (Feudtner C and Marcuse E, 2001). Another opposing view is that rather than comparing present vaccination costs to previous ones, it would be more judicious to compare vaccination to other health interventions, especially those targeted to sick people. In 2005 the Finnish government paid approximately 200 € for vaccines per each Finnish child up to 18 years of age (Table 3). This is in striking contrast to the funds spent by the state to cover medical expenses linked to diseases. For example, according to the National Health Insurance statistics, in 1 year alone, in 2005, for each of the 9% of Finns officially diagnosed with hyperlipidemia, the Finnish State paid 95–164 € in order to cover the costs of related medications (statins) alone. For such a comparison to be justified and seriously taken into account while resources are limited, a major shift of paradigm would need to take place. Are society and health-care professionals ready for it?

Conflict of interest statement The research team of the author has received research grants from Sanofi Pasteur, PATH and the European Commission DG Research. The author has served as technical expert and received honoraria from these tasks from GlaxoSmithKline, SBL vaccines and Wyeth as well as from governmental and international institutions.

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